



BILLING CODE 6560-50-P

## **ENVIRONMENTAL PROTECTION AGENCY**

### **40 CFR Part 180**

**[EPA-HQ-OPP-2014-0630; FRL-9934-17]**

### **Dimethyl sulfoxide; Exemption from the Requirement of a Tolerance**

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Final rule.

**SUMMARY:** This regulation amends the exemption from the requirement of a tolerance for residues of dimethyl sulfoxide (CAS Reg. No. 67-68-5) when used as an inert ingredient (solvent, co-solvent) in pesticide formulations applied to growing crops (pre-emergent use only) to include use after the crop emerges from the soil but before harvest provided that the potential for increased residues of the formulation's active ingredient(s) in or on food commodities has been assessed. ISK BioSciences submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), requesting an amendment to an existing exemption from the requirement of a tolerance. This regulation eliminates the need to establish a maximum permissible level for residues of dimethyl sulfoxide.

**DATES:** This regulation is effective [*insert date of publication in the Federal Register*].

Objections and requests for hearings must be received on or before [*insert date 60 days after date of publication in the Federal Register*], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

**ADDRESSES:** The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2014-0630, is available at <http://www.regulations.gov> or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at <http://www.epa.gov/dockets>.

**FOR FURTHER INFORMATION CONTACT:** Susan Lewis, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; main telephone number: (703) 305-7090; email address: [RDfRNotices@epa.gov](mailto:RDfRNotices@epa.gov).

## **SUPPLEMENTARY INFORMATION:**

### **I. General Information**

#### *A. Does this Action Apply to Me?*

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

*B. How Can I Get Electronic Access to Other Related Information?*

You may access a frequently updated electronic version of 40 CFR part 180 through the Government Printing Office's e-CFR site at [http://www.ecfr.gov/cgi-bin/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab\\_02.tpl](http://www.ecfr.gov/cgi-bin/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl).

*C. How Can I File an Objection or Hearing Request?*

Under FFDCA section 408(g), 21 U.S.C. 346a, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2014-0630 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or

before *[insert date 60 days after date of publication in the **Federal Register**]*. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing (excluding any Confidential Business Information (CBI)) for inclusion in the public docket. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit the non-CBI copy of your objection or hearing request, identified by docket ID number EPA-HQ-OPP-2014-0630, by one of the following methods:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be CBI or other information whose disclosure is restricted by statute.
  - *Mail:* OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.
  - *Hand Delivery:* To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>.
- Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

## **II. Petition for Exemption**

In the **Federal Register** of March 4, 2015 (80 FR 11611) (FRL-9922-68), EPA issued a document pursuant to FFDCA section 408, 21 U.S.C. 346a, announcing the filing of a pesticide petition (IN-10713) by ISK BioSciences, 7470 Auburn Rd., Suite A, Concorde, OH 44077. The petition requested that 40 CFR 180.920 be amended by modifying an exemption from the

requirement of a tolerance for residues of dimethyl sulfoxide (CAS Reg. No. 67-68-5) when used as an inert ingredient (diluent) at levels not to exceed 62% in pesticide formulations containing cyclaniliprole. That document referenced a summary of the petition prepared by ISK BioSciences, the petitioner, which is available in the docket, <http://www.regulations.gov>. There were no comments received in response to the notice of filing.

Based upon review of the data supporting the petition, EPA has modified the request for a tolerance exemption due to the concern regarding the chemical properties of dimethyl sulfoxide that may result in increased active ingredient residues. Therefore, the tolerance exemption under 40 CFR 180.920 was modified. This limitation is based on the Agency's risk assessment which can be found at <http://www.regulations.gov> in document Dimethyl sulfoxide; Human Health Risk Assessment and Ecological Effects Assessment to Support Proposed Exemption from the Requirement of a Tolerance When Used as Inert Ingredients in Pesticide Formulations in docket ID number EPA-HQ-OPP-2014-0630.

### **III. Inert Ingredient Definition**

Inert ingredients are all ingredients that are not active ingredients as defined in 40 CFR 153.125 and include, but are not limited to, the following types of ingredients (except when they have a pesticidal efficacy of their own): Solvents such as alcohols and hydrocarbons; surfactants such as polyoxyethylene polymers and fatty acids; carriers such as clay and diatomaceous earth; thickeners such as carrageenan and modified cellulose; wetting, spreading, and dispersing agents; propellants in aerosol dispensers; microencapsulating agents; and emulsifiers. The term "inert" is not intended to imply nontoxicity; the ingredient may or may not be chemically active. Generally, EPA has exempted inert ingredients from the requirement of a tolerance based on the low toxicity of the individual inert ingredients.

#### **IV. Aggregate Risk Assessment and Determination of Safety**

Section 408(c)(2)(A)(i) of FFDCA allows EPA to establish an exemption from the requirement for a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is “safe.” Section 408(b)(2)(A)(ii) of FFDCA defines “safe” to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.” This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408(b)(2)(C) of FFDCA requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to “ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue....”

EPA establishes exemptions from the requirement of a tolerance only in those cases where it can be clearly demonstrated that the risks from aggregate exposure to pesticide chemical residues under reasonably foreseeable circumstances will pose no appreciable risks to human health. In order to determine the risks from aggregate exposure to pesticide inert ingredients, the Agency considers the toxicity of the inert in conjunction with possible exposure to residues of the inert ingredient through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings. If EPA is able to determine that a finite tolerance is not necessary to ensure that there is a reasonable certainty that no harm will result from aggregate exposure to the inert ingredient, an exemption from the requirement of a tolerance may be established.

Consistent with FFDCA section 408(c)(2)(A), and the factors specified in FFDCA section 408(c)(2)(B), EPA has reviewed the available scientific data and other relevant

information in support of this action. EPA has sufficient data to assess the hazards of and to make a determination on aggregate exposure for dimethyl sulfoxide including exposure resulting from the exemption established by this action. EPA's assessment of exposures and risks associated with dimethyl sulfoxide follows.

#### *A. Toxicological Profile*

EPA has evaluated the available toxicity data and considered their validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. Specific information on the studies received and the nature of the adverse effects caused by dimethyl sulfoxide as well as the no-observed-adverse-effect-level (NOAEL) and the lowest-observed-adverse-effect-level (LOAEL) from the toxicity studies are discussed in this unit.

Dimethyl sulfoxide has low acute toxicity via the oral and dermal in rats and mice and inhalation route in rats. The acute oral lethal dose (LD)<sub>50</sub>  $\geq$  7,920 milligrams/kilograms (mg/kg) in rats and mice. The acute dermal LD<sub>50</sub>  $\geq$  40,000 mg/kg in rats and mice. The acute inhalation lethal concentration (LC)<sub>50</sub>  $\geq$  1,600 milligram/meter<sup>3</sup> (mg/m<sup>3</sup>) (~277 mg/kg) in rats. It is a dermal, eye and gastric irritant in rats and rabbits. It is a sensitizer in guinea pigs.

Overall systemic toxicity with regard to oral and dermal exposure to dimethyl sulfoxide is low. The target organ of toxicity is the eye. Changes in the eyes, such as refractile changes in the lens and lens composition are seen in various animals at doses above the limit dose (1,000 mg/kg/day).

Systemic toxicity is not observed following exposure to dimethyl sulfoxide at dose levels up to 1,000 mg/kg/day (the limit dose) in subchronic, chronic or reproduction/developmental

toxicity studies via oral, dermal or inhalation exposures in rats, dogs and rabbits. Dimethyl sulfoxide is not expected to be carcinogenic based on the lack of mutagenicity and the lack of tumor formation in cancer initiation/promotion studies. It is not neurotoxic nor immunotoxic.

Toxicity of dimethyl sulfoxide via the inhalation route of exposure is limited to portal of entry effects at 2.783 mg/l (equivalent to 722 mg/kg/day).

In the rat and monkey, dimethyl sulfoxide administered via the oral and/or dermal route is rapidly absorbed, metabolized and excreted. Excretion is primarily via urine, feces was a minor route in the rat only. The major metabolite was dimethyl sulfone. Dimethyl sulfide, another metabolite, is eliminated through the breath. There is no bioaccumulation.

Specific information on the studies received and the nature of the adverse effects caused by Dimethyl sulfoxide as well as the NOAEL and the LOAEL from the toxicity studies can be found at <http://www.regulations.gov> in the document "Dimethyl sulfoxide; Human Health Risk Assessment and Ecological Effects Assessment to Support Proposed Exemption from the Requirement of a Tolerance When Used as Inert Ingredients in Pesticide Formulations" in docket ID number EPA-HQ-OPP-2014-0630.

#### *B. Toxicological Points of Departure/Levels of Concern*

Once a pesticide's toxicological profile is determined, EPA identifies toxicological points of departure (POD) and levels of concern to use in evaluating the risk posed by human exposure to the pesticide. For hazards that have a threshold below which there is no appreciable risk, the toxicological POD is used as the basis for derivation of reference values for risk assessment. PODs are developed based on a careful analysis of the doses in each toxicological study to determine the dose at which no adverse effects are observed (the NOAEL) and the lowest dose at which adverse effects of concern are identified (the LOAEL). Uncertainty/safety factors are



used in conjunction with the POD to calculate a safe exposure level - generally referred to as a population-adjusted dose (PAD) or a reference dose (RfD) - and a safe margin of exposure (MOE). For non-threshold risks, the Agency assumes that any amount of exposure will lead to some degree of risk. Thus, the Agency estimates risk in terms of the probability of an occurrence of the adverse effect expected in a lifetime. For more information on the general principles EPA uses in risk characterization and a complete description of the risk assessment process, see <http://www.epa.gov/pesticides/factsheets/riskassess.htm>.

The available toxicity studies indicate that dimethyl sulfoxide has low toxicity. These data demonstrated adverse effects only at doses  $\geq 1100$  mg/kg/day (above the limit dose). Therefore, since no endpoint of concern was identified for dimethyl sulfoxide, a qualitative risk assessment is appropriate.

### *C. Exposure Assessment*

1. *Dietary exposure from food and feed uses.* In evaluating dietary exposure to dimethyl sulfoxide, EPA considered exposure under the proposed exemption from the requirement of a tolerance. EPA assessed dietary exposures from dimethyl sulfoxide in food as follows:

Dietary exposure can occur from eating foods containing residues of dimethyl sulfoxide. Because no hazard endpoint of concern was identified for the acute and chronic dietary assessment (food and feed uses, a quantitative dietary exposure risk assessment was not conducted.

2. *Dietary exposure from drinking water.* Since a hazard endpoint of concern was not identified for the acute and chronic dietary assessment, a quantitative dietary exposure risk assessment for drinking water was not conducted.

3. *From non-dietary exposure.* The term “residential exposure” is used in this document to refer to non-occupational, non-dietary exposure (e.g., textiles (clothing and diapers), carpets, swimming pools, and hard surface disinfection on walls, floors, tables).

Dimethyl sulfoxide may be used in consumer products that may be used around the home. However, based on the lack of toxicity, a quantitative exposure assessment from “residential exposures” was not performed.

4. *Cumulative effects from substances with a common mechanism of toxicity.* Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide's residues and “other substances that have a common mechanism of toxicity.”

EPA has not found dimethyl sulfoxide to share a common mechanism of toxicity with any other substances, and dimethyl sulfoxide does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that dimethyl sulfoxide does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see EPA's website at <http://www.epa.gov/pesticides/cumulative>.

#### *D. Safety Factor for Infants and Children*

1. *In general.* Section 408(b)(2)(C) of FFDCA provides that EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and

exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the FQPA Safety Factor (SF). In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

At this time, there is no concern for potential sensitivity to infants and children resulting from exposures to dimethyl sulfoxide. There is no reported quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to dimethyl sulfoxide in developmental toxicity studies in rats and rabbits. No quantitative or qualitative evidence of increased susceptibility has been reported following the pre/postnatal exposure to rats and rabbits in 2-generation reproduction toxicity studies in rats and rabbits. Given the lack of adverse toxicological effects at limit dose levels, a safety factor analysis has not been used to assess the risk. For these reasons the additional tenfold safety factor is unnecessary.

#### *E. Aggregate Risks and Determination of Safety*

EPA determines whether acute and chronic dietary pesticide exposures are safe by comparing aggregate exposure estimates to the acute PAD (aPAD) and chronic PAD (cPAD). For linear cancer risks, EPA calculates the lifetime probability of acquiring cancer given the estimated aggregate exposure. Short-, intermediate-, and chronic-term risks are evaluated by comparing the estimated aggregate food, water, and residential exposure to the appropriate PODs to ensure that an adequate MOE exists.

1. *Acute risk.* An acute aggregate risk assessment takes into account acute exposure estimates from dietary consumption of food and drinking water. No adverse effect resulting

from a single oral exposure was identified and no acute dietary endpoint was selected.

Therefore, dimethyl sulfoxide is not expected to pose an acute risk.

2. *Chronic risk.* Using the exposure assumptions described in this unit for chronic exposure, EPA has concluded that based on the low toxicity of dimethyl sulfoxide and since no chronic endpoint was identified, chronic risk is not expected.

3. *Short-term risk.* Short-term aggregate exposure takes into account short-term residential exposure plus chronic exposure to food and water (considered to be a background exposure level). Because no short-term adverse effect was identified, dimethyl sulfoxide is not expected to pose a short-term risk.

4. *Intermediate-term risk.* Intermediate-term aggregate exposure takes into account intermediate-term residential exposure plus chronic exposure to food and water (considered to be a background exposure level). Because no intermediate-term adverse effect was identified, dimethyl sulfoxide is not expected to pose an intermediate-term risk.

5. *Aggregate cancer risk for U.S. population.* Based on the lack of increased tumor formation in initiation/promotion toxicity studies and the lack of mutagenicity, dimethyl sulfoxide is not expected to pose a cancer risk to humans.

6. *Determination of safety.* Based on these risk assessments, EPA concludes that there is a reasonable certainty that no harm will result to the general population, or to infants and children from aggregate exposure to dimethyl sulfoxide residues.

## **V. Other Considerations**

### *A. Analytical Enforcement Methodology*

An analytical method is not required for enforcement purposes since the Agency is establishing an exemption from the requirement of a tolerance.

## **VI. Conclusions**

Therefore, an exemption from the requirement of a tolerance is established under 40 CFR 180.920 for dimethyl sulfoxide (CAS Reg. No. 67-68-5) when used as an inert ingredient solvent, cosolvent in pesticide formulations used before crop emerges from soil or prior to formation of edible parts of food plants; for pesticide formulations used after crop emerges but before harvest, provided that the potential for increased residues of the formulation's active ingredient(s) in or on food commodities has been assessed.

## **VII. Statutory and Executive Order Reviews**

This action establishes a tolerance under FFDCA section 408(d) in response to a petition submitted to the Agency. The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled "Regulatory Planning and Review" (58 FR 51735, October 4, 1993). Because this action has been exempted from review under Executive Order 12866, this action is not subject to Executive Order 13211, entitled "Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use" (66 FR 28355, May 22, 2001) or Executive Order 13045, entitled "Protection of Children from Environmental Health Risks and Safety Risks" (62 FR 19885, April 23, 1997). This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA) (44 U.S.C. 3501 *et seq.*), nor does it require any special considerations under Executive Order 12898, entitled "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations" (59 FR 7629, February 16, 1994).

Since tolerances and exemptions that are established on the basis of a petition under FFDCA section 408(d), such as the tolerance in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*), do not apply.

This action directly regulates growers, food processors, food handlers, and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled “Federalism” (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled “Consultation and Coordination with Indian Tribal Governments” (65 FR 67249, November 9, 2000) do not apply to this action. In addition, this action does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1501 *et seq.*).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA) (15 U.S.C. 272 note).

#### **VIII. Congressional Review Act**

Pursuant to the Congressional Review Act (5 U.S.C. 801 *et seq.*), EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of

Representatives, and the Comptroller General of the United States prior to publication of the rule in the **Federal Register**. This action is not a “major rule” as defined by 5 U.S.C. 804(2).

**List of Subjects in 40 CFR Part 180**

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: September 14, 2015.

G. Jeffery Herndon,

*Acting Director, Registration Division, Office of Pesticide Programs.*

Therefore, 40 CFR chapter I is amended as follows:

**PART 180--[AMENDED]**

1. The authority citation for part 180 continues to read as follows:

**Authority:** 21 U.S.C. 321(q), 346a and 371.

2. In §180.920, add alphabetically the inert ingredient “Dimethyl Sulfoxide (CAS no. 67-68-5)” to the table to read as follows:

**§ 180.920 Inert ingredients used pre-harvest; exemptions from the requirement of a tolerance.**

\* \* \* \* \*

Inert ingredients	Limits	Uses
***	*	***
Dimethyl Sulfoxide (CAS no. 67-68-5)	For pesticide formulations used before crop emerges from soil or prior to formation of edible parts of food plants; for pesticide formulations used after crop emerges but before harvest, provided that the potential for increased residues of the formulation's active ingredient(s) in or on food	Solvent or co-solvent



	commodities has been assessed.	
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